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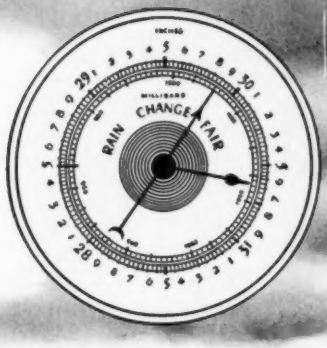

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EDITORIAL

A CHALLENGE TO THE WHOLESALER

NO ONE can deny that the wholesale druggists of America render a most important service in maintaining an efficient and effective drug distribution system in the United States. By means of wholesalers, located at strategic places throughout the country, pharmacists in almost every city and town are within a short distance of a well-stocked warehouse containing drugs and specialties collected and manufactured all over the world. In most of our large cities wholesalers pride themselves on their ability to ship an order the same day it is received. If pharmacists were obliged to order direct from each manufacturer or drug importer the delay would be considerable and a great inconvenience would be suffered by both manufacturer and pharmacist.

Wholesale druggists have also manifested a sincere interest in the pharmacist's welfare, both professional and economic, throughout the years; for indeed he is their customer, and unless he is prosperous they are not likely to be. The activities of the N. W. D. A. are ample evidence of its desire to be helpful to both pharmacists and pharmacy, and the late Dr. Newcomb was known and respected for his untiring efforts in behalf of American pharmacy.

With this defense of the integrity of purpose and essentiality of wholesaler service, we should now like to call attention to one defect in this service which needs correction.

Many pharmacists, today, are interested in preparing certain new products extemporaneously. The scientific and professional literature of pharmacy and medicine is replete with formulas for many new products such as, for example, dermatological vehicles; buffered, isotonic collyria; emulsions; sun-screening preparations, etc. The manufacture of these products requires certain chemicals, some official and others not, but in almost every instance the pharmacist finds that it is extremely difficult to obtain a source of supply. The manufacturers of these chemicals are usually unknown to the pharmacist, and even when they are finally identified it is difficult and sometimes impossible to purchase the small quantity of material which the average pharmacist needs.

Wholesalers have shown little interest in stocking these products since the demand is low and the turn-over not such as to warrant an inventory according to usual standards. The result is that many pharmacists are discouraged in their efforts to exercise professional skill and prepare special formulas in which they might readily interest their physician contacts. Actually, many pharmacists find it necessary to refuse certain modern prescriptions simply because they do not know where to obtain certain of the accessory ingredients.

Even certain official drugs in this category are not available from the average wholesaler and we might mention as examples: Polysorbate 80, Polyethylene Glycol 400, Polyethylene Glycol 4000, Polyethylene Glycol 400 Monostearate, Bentonite, Ozokerite, the Pharmagels, etc. Many others, often needed for special compounding, might be mentioned.

We should like to draw attention to the fact that insofar as this type of product is concerned an entirely different principle is involved than in the instance of some little used, obscure proprietary item. No damage is done the professional prestige of pharmacy if a physician prescribes some little known unimportant proprietary and the pharmacist cannot obtain it readily When, however, the physician reads in the medical literature of some new, excellent vehicle; prescribes it, and finds that his pharmacist not only doesn't have it but can't obtain it from his wholesaler, all of pharmacy is discredited, wholesaler and retailer alike.

Wholesale druggists have a responsibility in this matter, for they are not, or at least should not be, simply the distributing agents for the large manufacturing pharmaceutical houses. It is their duty to help the retailer in meeting his problems of supply even though at times it must be done at a net loss for certain items. We ask the wholesalers to whom this message is directed to consider carefully the full implications of the legend "not in stock" when stamped on the order of some enterprising, conscientious pharmacist who is trying to render professional service and raise the standards of our profession. Only by the understanding cooperation of the wholesalers can this problem be solved and pharmacy enabled to render the service to which it is pledged.

L. F. Tice

A COMPARATIVE STUDY OF THE EFFECTS OF PARA-AMINO SALICYLIC ACID AND THEPHORIN ON THE EMERGENCE OF STREPTOMYCIN RESISTANT SALMONELLA.

By Vivian Fromberg, A. B.[1]

THE value of para-aminosalicylic acid (PAS) in suppressing the emergence of streptomycin resistant strains of tubercle bacilli is now well established (Karlson, Pfuetze, Carr, Feldman and Hinshaw, 1949). In vitro experiments of Vennesland, Ebert and Bloch, 1948, have shown that in addition to the bacteriostatic effect of PAS itself (Pfuetze and Pyle, 1949) there is a synergistic action between streptomycin and PAS rendering the combination effective at subminimal levels of either alone.

Antihistaminics have been used in conjunction with streptomycin for the purpose of diminishing toxicity symptoms of the latter (Bignal and Crofton, 1949). While antihistaminics have been used in tuberculosis, their use has been confined primarily to the study of their effect on the tuberculin reaction (Graub and Barrist, 1950), (Hunter, Hyde and Davis, 1950). Although PAS has been shown to have some bacteriostatic effect on other organisms (Sievers, O., 1947), no work has been done on organisms other than the tubercle bacilli with special reference to the combined effects of PAS and streptomycin. It is the purpose of this paper to study the effect of PAS and one of the antihistaminics, Thephorin tartrate, both in relation to their synergistic action with streptomycin, and to the emergence of streptomycin resistant forms of *Salmonella typhimurium* 533.[2]

Experimental

Determination of the susceptibility of Salmonella typhimurium to streptomycin. In order to establish the susceptibility of the normal strain of *Salmonella typhimurium* to streptomycin the following procedure was used. To 9 ml. of nutrient agar, 1 ml. of varying con-

(1) Medical student, Woman's Medical College of Pennsylvania, Philadelphia, Pennsylvania.

(2) We are greatly indebted to Dr. H. H. Plough of Amherst College for the original culture of *Salmonella typhimurium*, 533.

centrations of pure dihydro-streptomycin hydrochloride [3] was added. Both pour plates and streak plates were used. For each pour plate, 0.1 ml. of a 1:10 dilution of a 24-hour culture was added to the streptomycin-agar mixture, and streak plates were made using a standard sized loop (3 mm.). Tube cultures were run simultaneously, using 0.1 ml. amounts of 24-hour culture diluted 1:10 and pipetted by micropipette into 5 ml. nutrient broth tubes. Plates and tubes contained streptomycin in increasing concentrations from 0 to 10,000 μg. per ml. At least five plates and five tubes were prepared at each concentration. All tube cultures were diluted 1:2 and read in a Klett-Summerson photoelectric colorimeter, using changes in turbidity after 24 hours as a measure of growth or inhibition in tube cultures. These were correlated with direct colony counts made on agar pour plates. It was found by both methods that growth of *Salmonella typhimurium* was only slightly inhibited by exposure to 10 μg. of streptomycin per ml., almost completely inhibited by 20 μg. per ml., and only rarely did a colony appear on plates containing 50μg. per ml. By selection of colonies from increasing concentrations, a strain was procured which was resistant to 10,000 μg. per ml. which may be considered for all purposes to be streptomycin fast.

Minimal bacteriostatic concentrations of PAS and Thephorin tartrate. The minimal bacteriostatic concentrations of PAS [4] and Thephorin tartrate [5] were determined by methods similar to those described above. One-half ml. of a 24-hour culture (*Salmonella typhimurium*) standardized at reading 220 (filter No. 42) on the K-S photoelectric colorimeter (the turbidity of uninoculated broth measuring 55) was added to varying concentrations of the drugs in nutrient broth to a total of 5 ml. A complete series was run on three different occasions in duplicate. Controls containing neither drug nor streptomycin were used in all experiments. It was found that Thephorin was completely bacteriostatic at a concentration of 333 μg. per ml. Slight cloudiness was noted in all tubes at 200 μg. per ml.; 100 μg. per ml. was moderately inhibitory, and 20 μg. per ml. ineffective. PAS was found to be completely bacteriostatic at a con-

(3) Squibb—All streptomycin in these experiments was pure base dihydrostreptomcyin hydrochloride.

(4) We are indebted to Merck and Company, Inc., Rahway, New Jersey for the generous supply of para-aminosalicylic acid used in these experiments.

(5) We are indebted to Hoffmann La Roche Inc., Nutley, New Jersey for supplying the Thephorin (2 methyl-9 phenyl-2,3,4,9 tetrahydro-1-pyridindene hydrogen tartrate).

centration of 666 μg. per ml., moderately inhibitory at 200 μg. per ml., very slightly inhibitory at 100 μg. per ml. and ineffective at 20 μg. per ml. (Compare with Table I.)

Determination of the synergistic effect of PAS and Thephorin in combination with streptomycin. Dosages chosen for the experiment were Thephorin 100 μg. per ml. and 20 μg. per ml.; PAS 200 μg. per ml., 100 μg. per ml. and 20μg. per ml. These were concentrations which were either moderately inhibitory or ineffective in themselves. These concentrations were combined with a minimally effective concentration of streptomycin (10 μg. per ml.) using 0.5 ml. of a 24-hour culture of *Salmonella typhimurium* standardized to a turbidity of 220 on the K-S photoelectric colorimeter. Four series were made on different days using the tube method described previously. The results of one series are given in Table I. Figures closely correlated with those presented were obtained in the other tests in this series.

TABLE I

The effect of combinations of streptomycin with Thephorin tartrate and para-aminosalicylic acid on the growth of *Salmonella typhimurium.*

Drug concentration, μg./ml.			
Streptomycin	Thephorin tartrate	para-amino-salicylic acid	*Density of culture
—	—	—	230
10	—	—	200
—	20	—	230
—	100	—	190
10	20	—	150
10	100	—	124
—	—	20	228
—	—	100	224
—	—	200	190
10	—	20	190
10	—	100	163
10	—	200	144

* Readings were made after 24 hours incubation at 37°C. Densities were determined by turbidity readings in the K-S photoelectric colorimeter after diluting all cultures 1:2.

The effect of previous exposure to Thephorin and PAS on the sensitivity of Salmonella typhimurium to streptomycin. A culture of *Salmonella typhimurium* was grown for 24 hours in varying concentrations of Thephorin and PAS before exposure to streptomycin. Three different series were made, 0.5 ml. of the same initial culture was incubated in tubes containing 20, 100 and 200 μg. per ml. of either Thephorin or PAS. After 24 hours at 37° C., all culture-drug mixtures were diluted with nutrient broth to equal concentrations of organisms as standardized by the K-S photoelectric colorimeter. Similar amounts of each mixture (0.1 ml.) were then plated in nutrient agar pour plates containing 20 μg. of streptomycin per ml., a convenient inhibitory concentration for colony counts. The results of two experiments are shown in Table II. Control plates prepared simultaneously without streptomycin, using 0.1 ml. of the diluted culture-drug mixtures, showed prolific growth, with the density of colonies so great as to render an accurate count impossible.

TABLE II

Sensitivity of *Salmonella typhimurium* to streptomycin after previous exposure to Thephorin tartrate and para-aminosalicylic acid (PAS).

Concentration of drug to which previously exposed μg./ml	Number of colonies on agar plates containing 20 μg. streptomycin/ml and 0.1 ml diluted drug-culture mixture	
	Experiment 1	Experiment 2
No previous exposure	28	13
Thephorin 20	24	2
" 100	6	2
" 200	4	0
PAS 20	100	not repeated
" 100	52	110
" 200	100	16

Tube cultures with Klett readings yielded results in approximately the same proportions.

Results similar to those reported above were likewise obtained with another strain of *S. typhimurium.*

Earlier experiments with *Salmonella typhosa* H901 whereby organisms incubated for 24 hours in varying concentrations of Thephorin

phosphate were subcultured on streptomycin plates, show results in accordance with those obtained above. The degree of streptomycin sensitivity varied directly with the increase in concentration of Thephorin.

In vivo experiments with mice. Animals were inoculated with *Salmonella typhimurium* intraperitoneally, followed several hours later by intraperitoneal injections of streptomycin, alone and in combination with PAS and Thephorin. The maximum non-toxic dosage of Thephorin was 2.5 μg. for a 20 gram mouse. Three to 5 μg. caused convulsions usually followed by death. The dose of PAS, brought to pH 6.5 with NaOH, was 7 μg. Two-tenth ml. of 5,000 μg. per ml. of streptomycin (1,000 μg.) was found to prolong life from 2 to 6 days although the animals eventually succumbed, whereas 2,000 μg. resulted in complete cure. All inocula were taken from 24-hour tube cultures standardized to 100 on the K-S photoelectric colorimeter and then diluted 1:10. Without drugs, death usually occurred in from 3 to 6 days. After establishing the desired dosage, a total of 40 mice were used including controls, those treated with streptomycin alone, and in combination with PAS and Thephorin for 3 successive days. No significant differences were observed when the drugs were used in combination. One thousand μg. of streptomycin whether used alone or in combination generally prolonged life up to two weeks. Eight of the 30 treated mice completely recovered. There is insufficient data to draw any conclusions concerning the in vivo effects of PAS and Thephorin on streptomycin resistance, but on the basis of this small series, no synergistic action can be claimed. It is to be noted that Williston and Youmans (1950) found that PAS proved to be ineffective in delaying the emergence of streptomycin resistant tubercle bacilli in mice.

Discussion

It is difficult to explain why after exposure to PAS the organisms appeared to be more resistant to streptomycin than the controls, as indicated in Table II. From this and previous studies of investigators, it may be concluded that PAS, a bacteriostatic agent in itself, merely enhances the activity of streptomycin when acting in combination with it. It has been postulated (Bloch, Vennesland, Ebert and Gomori, 1949) that PAS is capable of *selectively* sup-

pressing the growth of streptomycin resistant strains. Other studies have indicated that streptomycin resistant strains are only slightly more sensitive to PAS than the original strain, the inhibitory concentrations being in the same range. The exact nature of the mechanism by which streptomycin resistance is suppressed has not as yet been determined. It cannot be assumed that PAS in itself inhibits specifically resistant organisms. Thephorin, on the other hand, seems to exhibit a more pronounced effect in preventing the emergence of streptomycin resistant forms.

Acknowledgments

These experiments were done under the guidance of Ruth E. Miller, Ph.D., Professor of Bacteriology at the Woman's Medical College of Pennsylvania and with the technical assistance of Misses Evelyn R. Baker and Catherine Perry.

Summary and Conclusions

1. Both para-aminosalicylic acid and Thephorin tartrate when used in combination with streptomycin, effectively suppress the growth of *Salmonella typhimurium* in significantly smaller doses than required when either of these is used alone.

2. Previous exposure to Thephorin alters the organism in such a way as to render it more susceptible to streptomycin than the original strain. This was not found to be true in the case of para-aminosalicylic acid. These results suggest that further experimentation using Thephorin in place of para-aminosalicylic acid, might prove valuable in the treatment of bacterial infections with streptomycin.

3. In vivo experiments demonstrated no synergistic action between either Thephorin or para-aminosalicylic acid when administered with streptomycin.

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A SURVEY OF THE ANTIHISTAMINICS IN DENTISTRY

By M. M. Wolfred, R. M. Chamberlain, and T. N. Camberlain,*

A SURVEY of the literature indicates that there is a vast difference of opinion as to the occurrence of drug sensitivity, allergy, and histamine-like reactions in the field of dentistry. Numerous recent inquiries from various dental practitioners have stimulated this group to investigate the rate of occurrence of these reactions and their present mode of treatment. A summary of histamine-like conditions and methods for their control by the use of the antihistaminic drugs in Dentistry has been presented in a previous paper by Wolfred (1).

A conservative estimate of the number of hay fever victims in the United States is placed now at three per cent of the entire population, or considerably over 4,000,000 persons (2). This indicates that allergy is on the increase, as the above figure does not include other induced sensitivity reactions. This is becoming more of a problem to the dentist both in his practice and in the pre and post operative treatment of the patient. Swanson (3) has estimated the incidence of allergy in man to be 10-60 per cent, emphasizing the important part that this condition may play in the health problems of the oral cavity. However, despite the number of allergic persons, it has been assumed for some time that relatively few have had oral manifestations. Bearing this in mind, a survey was undertaken to determine whether or not allergy and other histamine-like reactions occurred often enough in the practice of dentistry to warrant precautionary measures.

A cross-section of the dentists in Southern California and Arizona was determined in an effort to obtain unbiased statistics representative of the average dental practitioner, rather than a specialized group such as the oral surgeons, exodontists, periodontists, etc.

The dental practitioners were picked at random and were interrogated by means of a survey questionnaire without personal identification. The questionnaire was constructed to state the purpose and use of such information as was required, and an arrangement was made so that the necessary data relating to the field of antihistaminics could be readily ascertained.

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Results

The survey is based on the results received from two hundred dental practitioners, representing graduates of twenty-seven institutions throughout the country. The dentists interrogated were found to have been in practice for an average of fifteen years.

TABLE I

COMPARISON OF YEARS IN DENTAL PRACTICE

Years	*Number*	*Percentage*
0-2	7	3.5%
3-5	33	16.5%
6-10	33	16.5%
11-15	26	13.0%
16-20	28	14.0%
20 +	73	36.5%

15 = Average Number of Years

The number of dentists who have or have not used antihistaminic drugs in their practice has been reported as follows:

TABLE II

Use Antihistaminic Drugs		*Have Not Used Antihistaminic Drugs*	
Number	Percent	Number	Percent
34	17.0	166	83.0

More than ninety per cent of the dentists requested further information concerning the use of antihistaminic drugs.

Data has been tabulated from the survey to demonstrate the occurrence and the types of sensitivity that the general practitioner has encountered.

For years various drugs have been reported in the dental literature as having caused sensitivity and allergy both to the patient and the practitioner. The per cent reporting sensitivity to drugs has been listed in Table III. A summary of the drugs producing sensitivity has been evaluated from the survey and is represented in Table IV, showing the relationship of reported occurrence to type of drug.

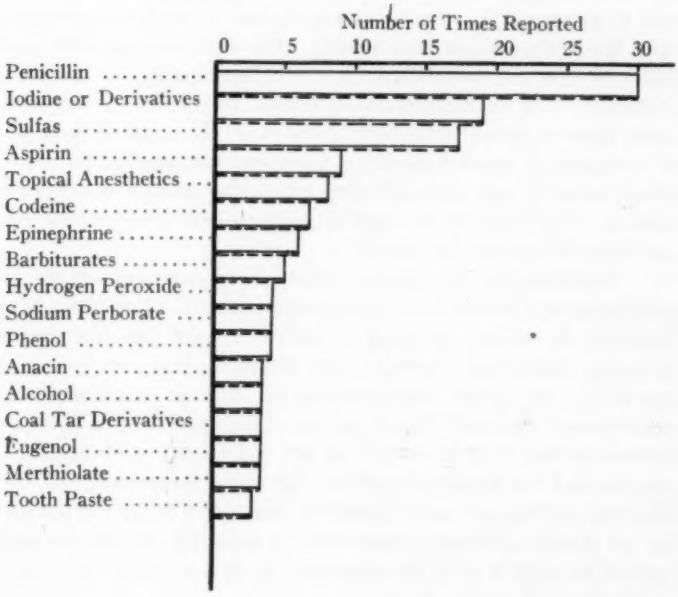
TABLE III

SENSITIVE AND ALLERGIC PATIENTS ENCOUNTERED BY THE GENERAL DENTAL PRACTITIONER

Types of Sensitivity	Percent Reporting				Frequency in Percentage of Those Reporting		
	No sensitivity		Sensitivity		Frequently	Occasionally	Rarely
	#	%	#	%			
Sensitivity to Amalgams	127	63.5%	73	36.5%	5.5	30.1	64.4
Sensitivity to Plastics	92	46.0%	108	54.0%	5.5	30.5	64.0
Sensitivity to Local Anesthetics	60	30.0%	140	70.0%	1.4	27.2	71.4
Asthmatic Patients	134	67.0%	66	33.0%	3.1	34.8	62.1
Sensitivity to Drugs	85	42.5%	115	57.5%	2.7	39.2	58.1

TABLE IV

SENSITIVITY TO DRUGS REPORTED



In addition, the following drugs have been reported: Sulfur, Silver Nitrate, Chlorophenol, Ammoniated dentifrices, Mercury derivatives, Silicate cements, Zinc chloride, Neo-synephrine, Aconite, Essential oils, Nicotinic acid and Chromic acid.

Discussion

The per cent of dental practitioners using antihistaminics to treat or prevent sensitivities is low compared to the number of sensitivities reported. This would indicate a further need for these drugs in dentistry.

The ability of the antihistaminic drugs to inhibit serous discharges from the respiratory mucous membranes, the cough reflex, post-nasal drip, etc., is not entirely limited to known allergic or sensitive patients. They can be used as an aid to treat the common cold which is one of the major reasons for the cancellation of dental appointments. According to the survey, fifty-four per cent of the dentists confronted with patients having a cold, attempt to extend the appointment, breaking up their chair time; twenty-two and one-half per cent accept the patient under duress, with ultraviolet radiation, use of gauze mask, volatile oil antiseptics, or no precautionary measures for their own personal health. The other twenty-three and one-half per cent use premedication and a combination of the above two methods. The antihistaminics compared to the common remedies for colds show superiority without irritation to the nasal mucosa, allowing it to function physiologically. Sufficient pre-medication with these drugs prior to appointment, may enable the dentist in many cases to receive his patient at the regular appointment time without hardship to either the patient or himself.

According to the survey, thirty-three per cent of the dentists encountered difficulties with asthmatic patients. The difficulties were reported as follows: gagging, interference with operative procedure, dyspnea, emotional nervous apprehension and tension, increased sensitivity to drugs, laryngiospasms, difficult breathing, choking, mucous and increased flow of saliva. One must bear in mind the usefulness of the antihistaminics as an aid in the prevention of these attacks and the elimination of the untoward symptoms. At the same time the practitioner must remember that these drugs are not ideal and do not work in all types of asthma. It is important that the asthmatic patient be helped with his symptoms so that operative procedure and chair time will not be wasted.

Summary

The results of this survey indicate that the incidence of sensitivity in dental patients occurs often enough to warrant precautionary measures in both pre and post operative treatment.

The unusual number of anaesthetic, plastic, amalgam, drug and asthmatic sensitivities would indicate the trial use of the antihistaminic drugs for their relief, until proper adjustments can be made.

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LABORATORY NOTES

Fasting and Traumatic Shock

STANDARD traumatic shock was produced in rats by the Noble-Collip drum (1) revolving at 40 r.p.m. Wistar male rats of 300 to 400 Gms. body weight were used. The animals were maintained on complete Rockland rat diet and water, in air conditioned quarters at 21° C. All experiments were performed at the same temperature. Table I gives the average survival time of normal and previously fasted rats, after being exposed to a total of 640 or 700 revolutions. During the fasting period, the animals had access to water *ad lib.*

TABLE I

AVERAGE SURVIVAL TIME IN HOURS

Group	Total Revolutions	
	640	700
Control	18	12.5
SE	2.11	2
N	6	10
Fasted 24 hours	3	2
SE	0.81	0.81
N	6	6
Fasted 48 hours	0.25	0.15
SE	0.25	0.068
N	2	4

From this data it may be concluded that fasting increases sensitivity to traumatic shock.

J. W. E. HARRISSON, J. L. AMBRUS, AND
E. DINER.

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Prevention of Proteus Hydrophilus Infections (Red Leg Disease) in Frog Colonies

SMITH (1) stated that he succeeded in curing *Proteus hydrophilus* infections (Red Leg disease) in *Bufo marinus* by administering 3 to 5 mg/100 Gm. Chloromycetin twice daily by gastric intubation. This author also suggested the use of Chloromycetin in the water of the storage tank of frogs to prevent Red Leg disease. However, he did not mention the desirable concentrations nor the result following.

We are using in our colony Chloromycetin in a concentration of 50 mg./liter in the water of the storage tank. After receiving the frogs from the dealer, they are washed daily for four days, then the Chloromycetin is added to the storage water. The water is changed every week, and the Chloromycetin is replaced at this time. For economical reasons, we are using 1 liter of water for 10-20 frogs. The animals are kept cool and in the dark all the time. Since this treatment was instituted, Red Leg disease has not occurred in our colony, whereas before this treatment, we had serious sporadic losses.

J. L. AMBRUS, C. M. AMBRUS, J. W. E. HARRISSON.

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Effect of Sodium Diethyl-dithio-carbamate on Thyroid Activity

FIFTEEN mice received daily subcutaneous injections of 50 mg/Kg. of sodium diethyl-dithio-carbamate over a period of 6 weeks. Autopsies were then performed, and the following observations noted: (a) test animals were in a poorer nutritional state than controls; (b) some abscesses were observed at the site of injections; (c) thyroids were greatly enlarged. Histological studies revealed a colloid-free goiter similar to those observed after prolonged treatment with thiouracil derivatives.

Several authors have attributed the antithyroid activity of thiouracil derivatives to the inhibition of certain enzyme systems. Schachner, Franklin and Chaikoff (1) assumed that these compounds inhibit

the cytochrome-cytochrome oxidase system, although Glock (2) could not confirm this hypothesis regarding cytochrome oxidase. Westerfeld and Lowe (3) and Dempsey (4) presumed that the peroxidase system is inhibited in the thyroid. Other authors (5, 6, 7, 8) assumed that a direct chemical reaction with thiouracil derivatives may interfere with thyroxine synthesis in the thyroid, rather than enzyme inhibition.

Because of the tendency of diethyl-dithio-carbamate to form complexes with metallic ions (copper, iron, zinc, cadmium, manganese, etc.), it seems possible that it may exert an antithyroid activity by inhibiting prosthetic groups of enzyme systems concerned in thyroxine synthesis. There is some evidence (9) that an enzyme containing copper may be involved in these functions.

The observed maximal tolerated dose of diethyl-dithio-carbamate is 60 mg/Kg. in mice; 30 mg/Kg. has almost no antithyroid activity.

C. M. Ambrus, J. L. Ambrus, J. W. E. Harrisson

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The Susceptibility of Hamsters Toward Infection by Tetanus Spores

IT is well-known that guinea pigs are highly susceptible to tetanus spores, while rats, and to a lesser degree mice, are relatively resistant. For this reason, guinea pigs are the animals of choice in diagnostic procedures for establishing the presence of *Cl. tetani.* Hamsters are relatively new laboratory animals, and to our knowledge there are no

publications concerning their sensitivity to tetanus spores. Since the use of hamsters is much more economical than that of guinea pigs, it seemed worthwhile to ascertain their suitability for tetanus tests.

The organism employed was *Clostridium tetani,* NIH strain, Tulloch, Type 11, obtained from the American Type Culture Collection, (catalog number 8033) and maintained by several passages in this laboratory.

Sharp wooden splinters were dipped into a concentrated suspension of washed spores, allowed to soak for 5 minutes, and inserted subcutaneously into each of the following animals:

2 male Sherman rats (80 Gm.)
6 male Syrian golden hamsters (60 Gm.)
2 male English smooth hair guinea pigs (200 Gm.)

The guinea pigs died, showing typical tetanic symptoms. The rats and hamsters showed no symptoms of tetanus infection, and continued to gain weight regularly during an observation period of three months.

H. Cravetz, J. L. Ambrus, J. W. E. Harrisson

Effect of Adenine on the Infection of Mice With Tetanus Spores

IT is a well-known fact that virulent tetanus spores, injected subcutaneously under aseptic conditions to mice, fail to induce the symptoms of tetanus. If, however, a solution of calcium chloride is injected simultaneously into the same site, symptoms will appear in a certain percentage of animals (1) (2) (5). Several theories have been offered to explain this phenomenon, none of which seem to be completely satisfactory. The infectivity of tetanus spores can also be increased by applying the spores by subcutaneously inserting wooden splinters, previously soaked in a suspension of tetanus spores.

In view of the fact that *Cl. tetani* requires adenine as a growth factor (3) it seemed to be of interest to test the effect of this substance on the susceptibility of mice to tetanus spores. Since tissue injuries and inflammatory processes cause the liberation of adenine derivatives, it is not impossible that calcium chloride and the insertion of wooden splinters act, in part, through the liberation of adenine. Furthermore, Howie and Cruickshank (4) described that adenosine triphosphate increases the susceptibility of mice to the spores of *B. anthracis.*

Swiss mice (females) from our own colony were used. The organism was *Cl. tetani,* NIH strain, Tulloch, obtained from the American Type Culture Collection, (catalog number 8033) and maintained by several passages in this laboratory. Four groups of five mice each were inoculated as follows:

Group I was injected subcutaneously under aseptic conditions with 0.2 ml. of a concentrated spore suspension.

Group II received an injection identical with that of Group I together with 100 mg/Kg adenine in 0.5 ml. of normal saline.

Group III also received the same injection as Group I, but with simultaneous injection of 125 mg/Kg of calcium chloride in 0.5 ml. of normal saline.

Group IV each animal had a wooden splinter, soaked in a suspension of concentrated tetanus spores, inserted into the right flank.

The occurrence of typical tetanic symptoms and of fatalities with tetanus symptoms which were observed during a three-week period are shown in the table below.

	Group Number			
	I (Control)	II (Adenine)	III ($CaCl_2$)	IV (Splinter)
Number showing tetanic symptoms without fatalities	0	3	1	1
Number of fatalities with tetanic symptoms	0	2	0	1

From these results it appears that adenine increases the susceptibility of mice to infection by tetanus spores. In these experiments, this action was more apparent than that elicited by calcium chloride or wooden splinters. This data must be considered preliminary and not therefore sufficient to prove the role of the liberation of adenine in the sensitizing effect toward tetanus spores of calcium chloride and tissue irritation by splinters.

H. Cravetz, J. L. Ambrus, C. M. Ambrus,
J. W. E. Harrisson.

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SELECTED ABSTRACTS

Therapeutic Use of Terramycin in Rickettsial Diseases. Smadel, J. E., Jackson, E. B., and Ley, H. L., Jr. *Ann. N. Y. Acad. Sci. 53*:375 (1950). Terramycin base, its hydrochloride, and its sodium salt were all effective in prolonging the life of embryonated eggs when injected ½ hour prior to inoculation with an infectious dose of scrub typhus. Even when injected 72 hours after inoculation with *Rickettsia tsutsugamushi* terramycin hydrochloride effectively delayed the death of the embryos. Comparative studies with aureomycin and chloramphenicol showed that terramycin was required in appreciably smaller amounts than either of the other antibiotics to inhibit *R. tsutsugamushi, R. rickettsii,* and *R. burneti* in embryos.

In mice infected with *R. tsutsugamushi* terramycin produced a rickettsiostatic action. One mg. of terramycin sodium daily prevented death in the mice when given from the 1st or 9th to the 21st day after inoculation but failed to have any beneficial effect when given from the day prior to inoculation until the 10th day after.

The authors also reported that 3 patients with scrub typhus received 3 Gm. of terramycin in a single oral dose while 3 other patients received 3 Gm. initially followed by 0.25 Gm. every 3 hours for 24 hours. Two of the patients on each regimen became afebrile within 72 hours but the fever persisted in the others. Chloramphenicol was given to one of those not benefited with a response to afebrile conditions within 20 hours.

Effect of Vitamin B_{12c} in Pernicious Anemia. Ungley, C. C. and Campbell, H. *Brit. Med. J.* No. 4699:151 (1951). The crystalline factor related to vitamin B_{12}, vitamin B_{12c}, was studied by the author first named, while the statistics were compiled by Campbell. Twenty-eight responses were observed on 24 patients since 4 patients received a second dose. A single dose was given to groups

of the patients at the rate of 10, 20, 40, 80, and 160 micrograms. Usual individual variations in red blood cell counts were observed in 15 days after the given doses but the mean of the 28 responses was almost identical with the response expected from equal doses of vitamin B_{12}. The log dose-response curve also did not significantly differ from that of vitamin B_{12}. A greater consistency of response was observed in doses of 40 micrograms and over and it was, therefore, suggested that such doses would be more useful than smaller doses.

When the red blood count rose to 4.5 million or more maintenance therapy was instituted. Twenty patients received 10 micrograms every two weeks but only 8 had been on maintenance therapy for more than six months. It was not necessary to raise the maintenance dose in any of the 20 patients but the author emphasized that for routine practice it was considered advisable to administer at least 60 micrograms every 3 weeks. All of the 20 patients in this study were closely observed and none had neurological complications. The results of maintenance dosage with vitamin B_{12_c} were also comparable to those expected with vitamin B_{12}.

Six patients with subacute combined degeneration of the spinal cord as a complication of pernicious anemia were studied as well as 8 patients with less involved neurological manifestations. None of the patients showed deterioration of their condition and only 2 remained unimproved. The author concluded that vitamin B_{12_c}, like liver extract and vitamin B_{12}, is capable of arresting the nervous lesions of pernicious anemia.

The author concluded that the results of the study failed to reveal any difference between the hemopoietic potency of vitamin B_{12_c} and vitamin B_{12} but, he pointed out that a large difference in dosage causes only a small increase in response. Further tests based upon hemoglobin content and the packed cell volume also failed to show any difference in potency between the two vitamins.

Diabetic Case Finding by the Anthrone Method. Fetz, R. H., and Petrie, L. M. *Pub. Health Rep. 65:*1709 (1950). In the field testing of individuals for the purpose of screening out the number who have diabetes an accurate but simple method is required. The authors investigated the use of the anthrone method on 749 persons.

Briefly, the anthrone method consists of adding 0.25 cc. of blood from the person to be tested to 2.25 cc. of a 5 per cent solution of trichloroacetic acid in water. To the supernatant liquid from this centrifuged suspension is added 5 cc. of anthrone reagent, prepared by dissolving 0.2 per cent of recrystallized anthrone in 95 per cent (v/v) sulfuric acid. This colored solution is then placed in a photoelectric colorimeter and read at a wave length of 620 millimicrons. This is a quantitative method but in the study reported by the authors the results were simply classified in 4 categories; I, less than 130 mg. per cent of blood sugar, II, 130 to 169 mg. per cent of blood sugar, III, 170 to 199 mg. per cent of blood sugar, and IV, 200 and over mg. per cent of blood sugar.

Follow-up glucose tolerance tests were run on 52 of the individuals and hyperglycemia was found in 20. Urine sugar determinations performed at the same time were negative in 10 of the 20. These findings caused the authors to discontinue the urine sugar test in favor of the anthrone blood sugar test as a mass survey screening procedure.

The authors concluded that the anthrone method gives results comparable with those obtained with other accepted methods and that it combines with this accuracy simplicity of procedure. It was possible for 3 technicians withdrawing blood samples, one technician pipetting, and 2 technicians actually conducting the test to perform 100 tests per hour.

Observations Following Treatment of Neurosyphilis With Penicillin. Curtis, A. C., Kruse, W. T., and Norton, D. H. *Am. J. Syph. Gonor. Ven. Dis. 34*:554 (1950). Penicillin in aqueous solution was injected intramuscularly in doses of 40,000 units every 3 hours for 12½ days to a total dose of 4,000,000 units. A portion of the patients treated also received concomitant fever therapy induced by tertian malaria, with 50 or more hours of fever. A total of 639 patients with neurosyphilis were treated by the authors. Among these patients 430 were observed for 1 to 5 years after a single course of treatment, 81 were re-treated elsewhere, 31 died, and 97 were lost to follow-up or were observed for less than 9 months. Of the 430 patients observed 221 had received penicillin therapy alone and 209 had received the combined treatment.

The spinal fluid cell counts, total protein determinations, colloidal gold tests, and quantitative Kahn reactions were approximately the same for the patients in the two treatment groups Among those patients observed for 4 to 5 years the Kahn tests had become negative in 41.3 per cent of the group treated with penicillin alone and in 38.7 per cent of those receiving the combined treatment. Those patients having paresis or taboparesis showed negative Kahn tests in 22.7 per cent and 40 per cent of the cases, respectively. The clinical results were evaluated on the basis of the patient's ability to continue his pretreatment occupation. These results were classified as excellent among the patients who had meningovascular neurosyphilis. Thirteen of the 19 given penicillin alone and 12 of the 13 receiving the combined treatment for tabes dorsalis were able to work, while in the group with paresis and taboparesis 17 of 20 given penicillin and 12 of 24 given the combined treatment were able to follow their occupation. The poorer results shown with the pencillin plus malaria treatment in the latter case was explained by the authors on the basis of the fact that usually the patients with the most severe involvement were given the combined treatment. Of the 31 deaths 16 were directly attributable to syphilis or had syphilis as a contributing factor.

The authors concluded that penicillin alone is probably adequate for the treatment of all types of neurosyphilis with the possible exception of severe paresis and primary optic atrophy.

Clinical Experience With Terramycin Hydrochloride. Linsell, W. D. and Fletcher, A. P. *Brit. Med. J.* No. 4690:1190 (1950). Terramycin hydrochloride has been shown to be quite stable in aqueous solution. The hydrochloride at a pH of 2 will retain its potency in aqueous solution for about 30 days when stored at 0° C. The sodium salt at a pH of 8.5 will retain its potency for about 7 days when stored at the same temperature. Solutions in human serum were about of equal stability.

Clinical studies revealed that terramycin was readily absorbed from the alimentary tract. A total dosage of 70 mg. per Kg., orally, each day given in divided doses at 6 hour intervals will give maximal blood levels even for severe infections. Some patients will attain such levels on doses as low as 50 mg. per Kg. Because of the high con-

centration of the antibiotic excreted in the urine adequate levels can be obtained with even smaller doses than 50 mg. per Kg. High concentrations were also obtained in the faeces. A dose of 66 to 87 mg. of the antibiotic per Kg. daily produced levels in the faeces within 24 hours ranging from 500 to 4,000 micrograms per Gm. From such high levels it was readily understandable that marked changes in the intestinal flora were obtained.

All of the common urinary pathogens were found to be sensitive to terramycin with the exception of *Pseudomonas pyocyanea* and *Proteus vulgaris*. The former also appeared to be amenable to treatment when high dosage was given, resulting in urine levels of 300 to 400 micrograms per cc. The pH of the urine seemed to have no effect on the results. The high concentrations obtained in the faeces gives promise of further safety control for intestinal surgery and further enhancement of the management of intestinal infections.

The authors stated that they had not observed any marked difference between terramycin and aureomycin except that terramycin is more effective against *Ps. pyocyanea* and is more stable in solution.

The most prominent side reaction was that of gastrointestinal disturbance, which occurred in 13 of 33 patients having courses lasting for 5 or more days. However, in only one case was it necessary to discontinue treatment.

The Stability of Sulfonamide Injections. Whittet, T. D. *Pharm. J. 165*:309 (1950). Solutions of the sodium salts of sulfacetamide, sulfadiazine, sulfamerazine, sulfamethazine, sulfapyridine, and sulfathiazole are all sensitive to light. Such solutions rapidly darkened to a yellow to reddish-brown color within one month when exposed to direct sunlight in the presence of oxygen. Storage in diffused light or in the dark retarded the rate of discoloration. There was found to be an appreciable darkening in the color of ampuls containing solutions of the sulfonamides immediately after autoclaving at 115° C. for 30 minutes when the ampuls were air-filled, but there was no appreciable change when the ampuls were nitrogen-filled. The author found also that the nitrogen-filled ampuls, with the exception of sulfacetamide and sulfathiazole, did not darken when stored in direct sunlight for a period of one month. In diffused light or in the dark there was no darkening within a year.

A further study of the effect of the replacement of air with nitrogen in ampuls containing solutions of the sodium salts of sulfacetamide and sulfathiazole showed that darkening was retarded but not prevented. The retarding effect was somewhat greater with sulfacetamide than with sulfathiazole. Previous experience had shown that 0.5 per cent of sodium meta bisulfite would prevent discoloration of solutions of sulfacetamide for about a year when stored in diffused light, but provided no protection in direct sunlight. The author thus suggested there would appear to be a two-fold cause for the discoloration in solutions of sulfacetamide, and possibly in sulfathiazole: oxidation and the action of direct sunlight.

The author quoted a number of studies that had been made on discolored solutions of the sulfonamides. These studies seemed to indicate that there was no significant increase in toxicity nor decrease in activity of the discolored solutions as compared with the fresh, colorless solutions.

The sodium salt of some of the sulfonamides had to be prepared by interaction with the calculated amount of sodium hydroxide. No difficulty was encountered in their preparation but the author pointed out that the pH of all solutions of sodium salts of the sulfonamides must be carefully checked. The pH of several of these solutions was determined electrometrically according to the following table.

Sodium Salt	pH
Sulfacetamide, 30 per cent	9.00
Sulfacetamide, 10 per cent	8.80
Sulfadiazine, 25 per cent	9.74
Sulfamethazine, 33.3 per cent	10.38
Sulfamerazine, 20 per cent	11.40
Sulfamerazine, 5 per cent	9.32
Sulfathiazole, 20 per cent	9.50

The author found that it was not possible to prepare a 30 per cent solution of the sodium salt of sulfathiazole. Crystals always reappeared after cooling. The most concentrated solution that could be prepared was 25 per cent at 15.5° C. and 20 per cent at room temperature. He, therefore, suggested that the solubilities given by the B. P. C. (1:3) and by the U. S. P. XIV (1:2.5) are incorrect.

It had been reported that the crystals formed following autoclaving or other heating of solutions of sulfathiazole sodium were de-

composition products. The author, therefore, tested the crystals which reappeared upon cooling following the heating for solution of the 30 per cent solution, and also the crystals obtained by cooling below room temperature a 20 per cent solution. These crystals responded to the identity tests for sulfathiazole sodium of the B. P. Nitrogen-filled ampuls of a 10 and of a 20 per cent solution of the salt were also prepared. Half of the ampuls were autoclaved and half were not. All were examined periodically for a period of two months and none of the ampuls showed any opalescence, crystal deposits nor other indications of deterioration. No evidence was thus found to indicate that heating caused a decomposition of the salt.

The Effect of Ascorbic Acid on the Healing Rate of Corneal Ulcers. Boyd, T. A. S. and Campbell, F. W. *Brit. Med J.* No. 4689:1145 (1950). A group of 50 patients with corneal ulcers were subdivided into two groups, one group of 28 patients received no ascorbic acid other than that contained in their normal diet. The second group of 22 patients received a daily supplement of 1.5 Gm. of ascorbic acid. The ascorbic acid content of the diet of all patients was apparently adequate for normal conditions since there was no evidence of scurvy in any of the patients.

There was no significant effect on the rate of healing of superficial ulcers from the therapy with massive doses of ascorbic acid. However, deep corneal ulcers showed a definite acceleration of epithelialization with supplemental ascorbic acid. The mean healing time in 11 patients with deep ulcers who received the massive doses of ascorbic acid was 4.36 days as compared with 6.15 days in 13 patients receiving no supplement of vitamin C. The depth of the ulcer and the degree of healing was determined from the intensity of fluorescence following the instillation of a 2 per cent aqueous solution of sodium fluorescein.

The authors stated that the nature of this action was not known but that it seemed evident that the vitamin had a value in therapy apart from its normal role as a vitamin at accepted levels of intake. It may be that there is a local deficiency of the vitamin at the site of any collagenous tissue lesion. If this were true then there would be benefit from the increased rate of diffusion which would occur from a high blood level of ascorbic acid.

The Local Application of Cortisone Acetate. Spies, T. D. and Stone, R. E. *South. Med. J. 43*:871 (1950). The effect of the local application of synthetic cortisone acetate on the lesions of iritis and uveitis, of allergic dermatitis, and of psoriasis were studied by the authors. Two patients with rheumatoid arthritis associated with iritis and uveitis, two with articular disability and allergic dermatitis, and two with typical chronic psoriasis were treated. All six of the patients had failed to respond to 3 distinct antihistaminic compounds.

An ophthalmic ointment containing 25 mg. of cortisone acetate per Gram brought about clearing of the eyes of both patients with iritis and uveitis by the sixth day of local application. Thirteen days of treatment with a cortisone acetate ointment brought about complete clearing of allergic dermatitis. The patients with psoriasis were treated with 3 courses of intramuscular cortisone acetate in doses of 1200 mg., 300 mg., and 375 mg., respectively. During the nine weeks in which these 3 courses were administered the lesions subsided from 70 to 95 per cent, with the most pronounced clearing occurring in the lesions of the scalp and on the surfaces of the elbows. In one case, a large lesion below the knee was treated by the topical application twice a day of an ointment containing 5 mg. of cortisone acetate per Gram. After 24 days of treatment the lesion showed as much clearing as had followed injections of cortisone, while the untreated lesions remained unchanged or had become worse.

The authors concluded that the finding that one lesion can be improved by local treatment with cortisone acetate without measurable changes in other lesions of the body is an important contribution toward the understanding of the pathogenesis of these conditions. The hypothesis that cortisone plays a fundamental role in the enzymatic process of all cells has gained support through the results obtained with these patients. Many opportunities for practical therapeutic application have thus been opened.

BOOK REVIEWS

The Story of California Pharmacy. By George Griffenhagen. Published by the American Institute of the History of Pharmacy, c/o College of Pharmacy, University of Wisconsin, Madison 6, Wisconsin. $1.00

Published in connection with the centenary of California's statehood (1950), this 58-page booklet is the first of a series of pamphlets through which the Institute plans to relate the pharmaceutical history of every State in the Union.

This initial work is quite interesting and apparently very complete. It contains a number of suitable illustrations, an excellent chronology, a good list of references to other sources of information on the same subject, and a long roster of the pioneer pharmacists in the Golden State. An index helps the reader find data of particular interest.

JOHN E. KRAMER

The Art of Compounding. By Glenn L. Jenkins, Don E. Francke, Edward A. Brecht and Glen J. Sperandio. Eighth Edition, 515 pages incl. index, 77 illustrations. The Blakiston Company, Philadelphia. $7.50.

This is the eighth edition of the book originally written by Dr. Scoville. It has as its authors four well known figures in American pharmacy. They have completely revised the book, having rewritten all the sections to bring them up to date. Classes of prescription products are presented in an orderly sequence leading from relatively simple to difficult preparations. There are many improvements in the present edition as compared to the previous one, but there are also some places where there are shortcomings. Some of these improvements and shortcomings will be discussed.

The chapter, *The Prescription,* has included in it an excellent table of veterinary doses, which will prove especially valuable to students and practicing pharmacists in certain areas. However, it is the reviewer's belief that the discussion on the pricing of prescriptions is much too brief and could be markedly improved.

There has been good revision in the chapters, *Tablets* and *Parenteral Solutions.* There is now an excellent review on tablet coatings

in the former, and a good discussion on the formulation and preparation of 29 parenteral solutions in the latter.

One of the most improved sections is the one entitled, *Adjusted Solutions*, in which there is a fine theoretical discussion on the adjustment of solutions to isotonicity and pH. More importance is attached to buffer solutions and the applications of pH in pharmacy.

The latest theories applying to solutions for the eye, nose, mouth, throat, lungs and enemas are included in the new chapter, *Solutions for Special Application*, but the discussion on douche preparations is lacking in present-day concepts. Another chapter new to this edition is *Allergenic Solutions*. The preparation, storage and dispensing of allergenic products are well covered.

There are shortcomings in the chapter, *Emulsions*. Too little mention is made of the anionic, cationic and non-ionic emulsifying agents. There is an insufficient discussion on the properties of emulsions and the factors influencing their stability.

Upon reading through the new edition, one quickly notes the improvement in the chapter, *Sterilization and Disinfection*. There is a much more complete discussion brought forth on the present methods utilized in sterilization procedures than appeared in the previous edition.

Keeping abreast with present-day pharmacy, there is excellent revision in the chapters dealing with incompatibilities, especially the one entitled, *Organic Incompatibilities*, in which the antibiotics, hormones and vitamins are discussed for the first time in some detail. In order to keep up with the trend of the use of proprietary medicinals in the compounding of prescriptions, a list of the commonly used trade name preparations, which are prescribed often in combinations with other medicaments, is presented with a qualitative statement of their ingredients. It is the authors' hopes that this listing will aid the student and practicing pharmacist diagnose any possible incompatibilities involving these preparations. Although the list is brief, it will serve as an aid; however, a quantitative statement for each proprietary would be of greater value yet.

The eighth edition has met the challenge of keeping up with the new trend in modern dispensing pharmacy. It is a text well recommended for the undergraduate pharmacy student and the dispensing pharmacist.

MARTIN BARR

Heterocyclic Compounds (Volume 2). Edited by Robert C. Elderfield, Ph. D.. 571 pages, 1951. John Wiley & Sons, Inc., New York. $15.00.

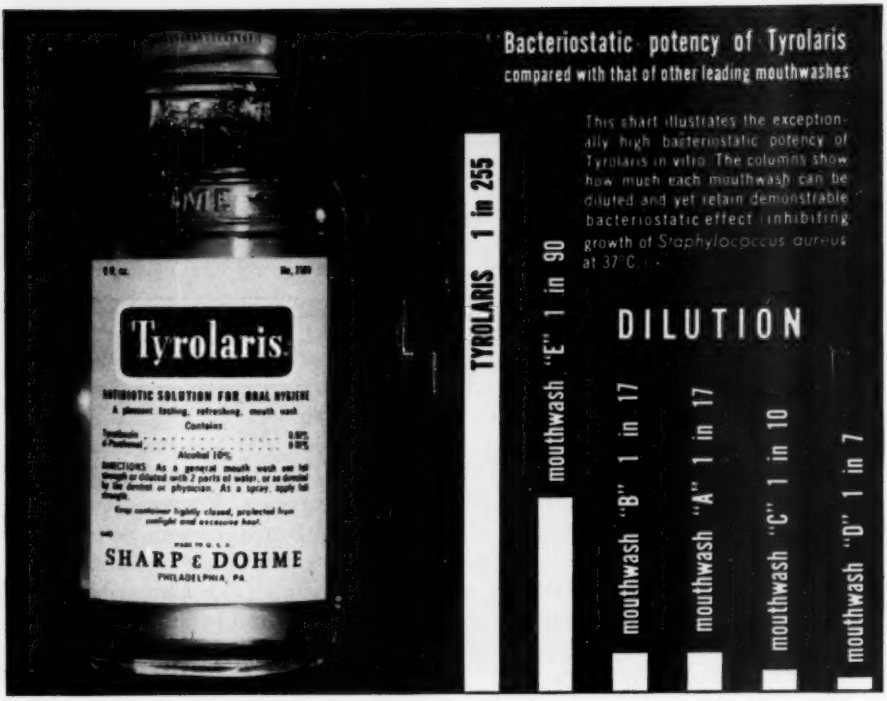
The first volume in the series *Heterocyclic Compounds,* published early in 1950, describes monocyclic compounds containing one hetero atom (oxygen, nitrogen, sulfur). This second volume covers polycyclic five- and six-membered compounds containing one oxygen or sulfur atom.

Although the breakdown is admittedly arbitrary, classification of the compounds discussed is achieved through grouping into chapters bearing the following headings: (1) Benzofuran and Its Derivatives; (2) Isobenzofuran, Phthalan, and Phthalide; (3) Dibenzofuran (Diphenylene Oxide); (4) Thionaphthene; (5) Dibenzothiophene; (6) Coumarins; (7) Isocoumarins; (8) Chromones, Flavones, and Isoflavones; (9) Chromenols, Chromenes, and Benzopyrylium Salts: The Anthocyanins; (10) Chromanones, Flavanones, Chromanols, and Flavanols; Catechin, Brazilin, and Hematoxylin; (11) Chromans; (12) Xanthones, Xanthenes, Xanthydrols, and Xanthylium Salts; (13) Fluorans, Fluoresceins, and Rhodamines; (14) Thiochromans and Related Compounds.

As in Volume 1, emphasis is placed on a discussion of the chemical principles of the substances included in the book, rather on an extensive presentation of their physical constants. Sulfur compounds are treated in somewhat less detail than their oxygen analogs since the chemistry of the former parallels that of the latter.

Authors of the chapters in this volume are Robert C. Elderfield, Victor B. Meyer, William E. Parham, David K. Fukushima, Stanley Wawzonek, and D. Stanley Tarbell—all acknowledged as experts in their respective fields of specialization. They have critically evaluated the extensive and widely disseminated material available for study, and then prepared a masterful and well-written survey of this branch of the chemistry of heterocycles.

ARTHUR OSOL



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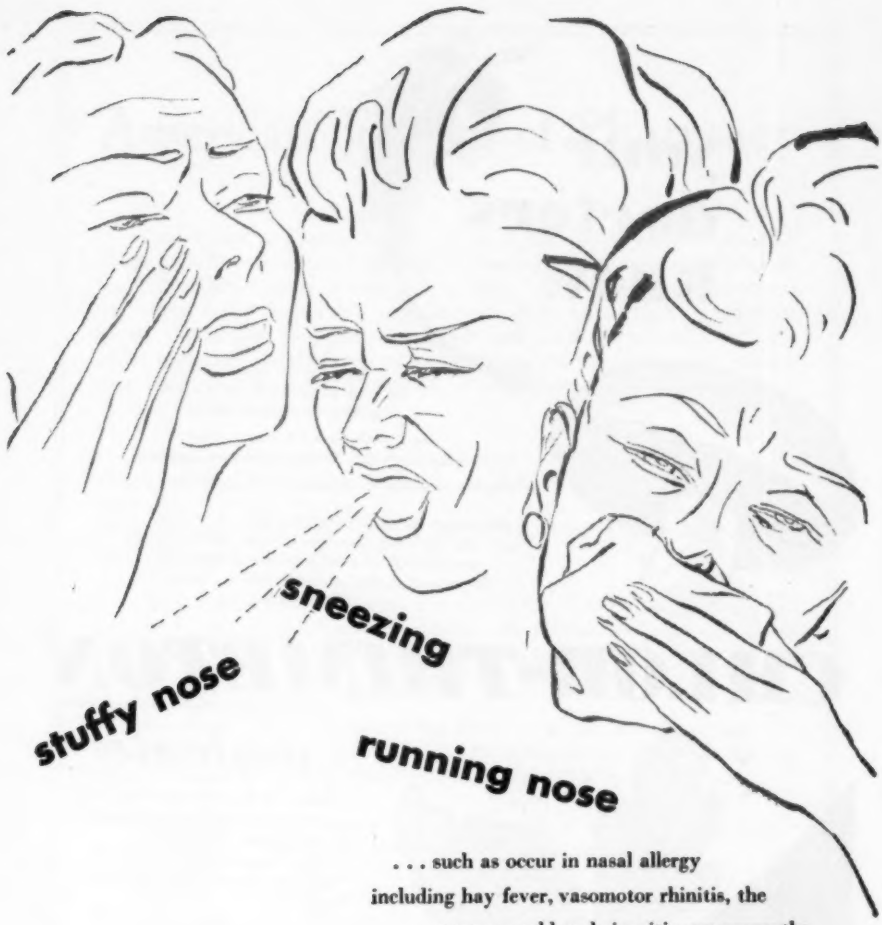

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